PERSPECTIVES: GENETICS

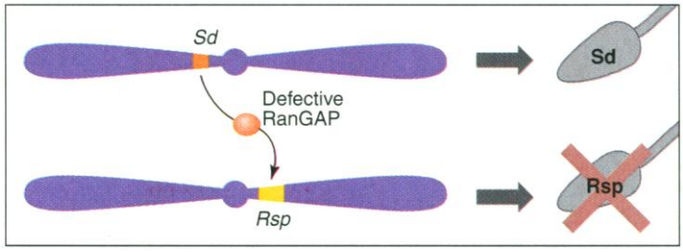
Unmasking a Cheating Gene

James F. Crow

The precision of meiosis—the two cell divisions that ensure that each sperm or egg gets only one member of each chromosome pair—keeps a tight rein on all genes, ensuring that the Mendelian lottery is scrupulously fair (*1*). Yet there are occasional cheaters that manage to beat the system and subvert it to their own advantage (*2*). The gene *Segregation distorter* (*Sd*) in the fruit fly *Drosophila* is a classic example. In heterozygous males that carry one copy of the mutant *Sd* gene and one copy of the normal gene, *Sd* is transmitted to practically all of the progeny rather than the canonical one-half. It does this by inducing those sperm that receive the homologous chromosome (which does not carry *Sd*) to self-destruct, leaving only those carrying *Sd* to survive and carry on the job of reproduction. Although the genetic rules by which *Sd* operates are well established, the molecular understanding of how *Sd* elicits such genetic favoritism has proved discouragingly elusive. On page 1742 of this issue, Merrill and colleagues (*3*) report a molecular breakthrough. They demonstrate that the product encoded by *Sd* is an abnormal, shortened version of RanGAP, a GTPase (guanosine triphosphatase)–activating protein that is critical for transporting materials into and out of the nucleus.

The *Sd* story began in 1956. That year my student, Motoo Kimura (later famous for the neutral theory of molecular evolution), returned to Japan and sent Yuichiro Hiraizumi in his place. Hiraizumi began an experiment that involved mating heterozygous male flies—carrying a chromosome from a wild *Drosophila* population and a chromosome bearing the eye-color marker genes *cinnabar* (*cn*) and *brown* (*bw*)—with homozygous females carrying *cn* and *bw* on both chromosomes. The combination of *cn* and *bw* produces white eyes. Among several hundred wild chromosomes tested, six produced almost no white-eyed progeny instead of the expected half. Somehow the wild chromosome prevented the *cn*/*bw* chromosome from being transmitted. Because distorted Mendelian ratios can be detected only when there are marker genes, this striking phenomenon had gone unnoticed throughout the decades of *Drosophila* research.

Earlier, Sandler and Novitski coined the expression "meiotic drive" to describe a situation in which meiosis is subverted to favor a particular gene. Sandler and Hiraizumi joined forces to show that the distortion occurred only in males, that the distorting system was found in *Drosophila* throughout the world, that the *Sd* chromosomes typically had inverted DNA sequences, and that the homologous chromosomes differed in their sensitivity to *Sd*. Genetic analysis of *Sd* was complicated by several DNA inversions, which prevented the mapping of its location by recombination analysis (*4*, *5*). The target site on the non-*Sd* chromosome was identified and named *Responder* (*Rsp*). They even constructed a suicide chromosome by moving a sensitive *Rsp* to the *Sd* chromosome. The *Sd* now disabled its own chromsome instead of the homologous chromosome. Of course, such a chromosome would never be found in nature; if it did occur it would be quickly eliminated.



Distorting gene segregation. During sperm development, the mutant *Sd* gene usually prevents spermatids that receive the homologous chromosome—which bears the *Sd*-sensitive target gene, *Rsp*—from reaching maturity. *Sd* spermatids develop into normal sperm, and thus, almost all the offspring inherit the *Sd* chromosome. It turns out that *Sd* encodes a defective RanGAP protein, the normal version of which is involved in transporting proteins into and out of the nucleus. Exactly how defective nuclear transport translates into nonmaturation of *Rsp* spermatids is still not known.

A few years later, Hiraizumi and Hartl showed that the distorted ratios were caused by the failure of sensitive *Rsp* sperm to mature. Shortly thereafter, Tokuyasu published electron micrographs in which half of the *Rsp* spermatids were visibly abnormal. Somehow, *Sd* prevents spermatids carrying the sensitive *Rsp* gene from maturing (*2*, *4*, *5*).

Lyttle used radiation to induce chromosome rearrangements and to move *Sd* and *Rsp* around the *Drosophila* genome. Translocation of *Rsp* to the sex chromosomes produced bizarre sex ratios, showing that *Rsp* does not have to be in its normal position in order to respond to *Sd*. Furthermore, *Sd* can also be moved around the genome but still retains its effect on *Rsp*. Among other things, Lyttle found that, remarkably, when the chromosome was broken at the *Rsp* locus, both pieces were sensitive to *Sd*. Thus, *Rsp* must be composed of at least two parts, and probably more.

Next came the cloning of *Rsp*, which seemed feasible because of its suspected repeat structure. Wu's analysis showed that *Rsp* was a chain of AT-rich, 120–base pair repeats (*4*). The number of repeats varied from less than 20 to thousands, and the larger the number the more sensitive *Rsp* was to *Sd* and the less viable were the *Rsp* spermatids.

This raised the question of why the sensitive *Rsp* locus is not eliminated by competition from target loci insensitive to the distorting activity of *Sd*. From a theoretical analysis of the dynamics of the system, it was suspected that sensitive *Rsp* is favored in the absence of *Sd*. This was later confirmed in Wu's population experiments. When he raised flies carrying sensitive *Rsp* chromosomes together with those carrying insensitive *Rsp* chromosomes in a population cage, the sensitive chromosomes invariably increased in number at the expense of the insensitive chromosomes (*2*, *4*).

Sandler's group identified a second locus, very close to *Sd*, that enhances the degree of distortion, and that was later shown to have minor distorting effects of its own (*4*). The reason for the DNA inversions in *Sd* became clear: they keep the components of the system together and prevent sensitive *Rsp* from crossing over into the *Sd* chromosome during meiosis, which would result in suicide of *Sd* spermatids.

Yet the main actor, *Sd*, remained recalcitrant although the *Sd* region was eventually cloned (*4*, *5*). Finally came the breakthrough. As reported in this issue (*3*), the *Sd* product turns out to be a defective version of a RanGAP protein. As it must, if it is to affect sperm maturation, this product is expressed in the testes. But how do *Sd* and *Rsp* interact to cause

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sperm dysfunction? Ran is a nuclear GTPase involved in transporting molecules into and out of the nucleus. Its enzymatic activity is greatly stimulated by another protein, RanGAP. It is reasonable to assume that defective RanGAP encoded by the *Sd* gene somehow interferes with nuclear transport in spermatids carrying a sensitive *Rsp* gene. The precise molecular mechanism by which the abnormal RanGAP causes this selective sperm dysfunction is not known. So, the mystery of segregation distortion is not yet solved. But the identification of the *Sd* gene product opens the way to a molecular understanding of this puzzle that has kept talented scientists around the world busy for 40 years.

References

1. J. F. Crow, *Bioessays* **13**, 305 (1991).
2. T. W. Lyttle, *Annu. Rev. Genet.* **25**, 511 (1991).
3. C. Merrill, A. Bayraktaroglu, A. Kusano, B. Ganetzky, *Science* **283**, 1742 (1999).
4. R. G. Temin *et al.*, *Am. Nat.* **137**, 287 (1991).
5. T. W. Lyttle, *Trends Genet.* **9**, 205 (1993).

PERSPECTIVES: MANTLE CONVECTION

A Thermal Balancing Act

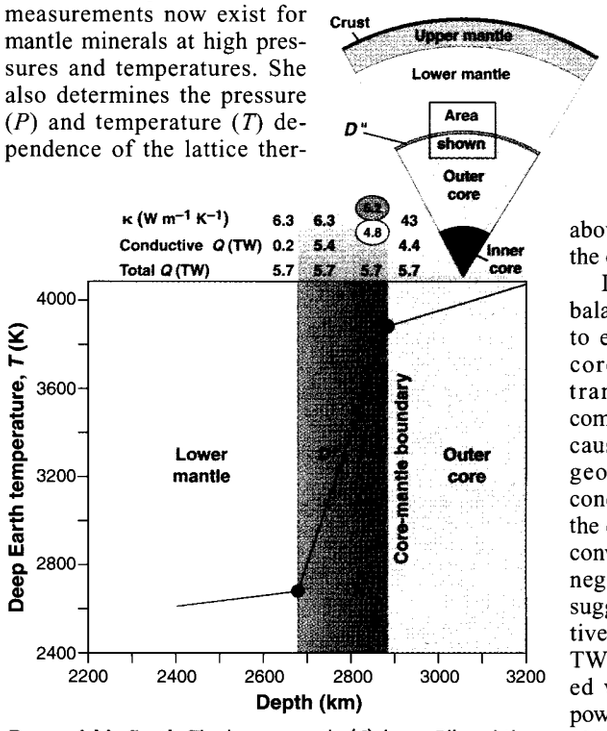
Orson L. Anderson

Earth core physicists have long faced a conundrum. The power, that is, the heat flow multiplied by the surface area, from Earth's core appears to greatly exceed the conductive capacity of Earth's mantle to carry it all away. This arises because the thermal conductivity, κ, of the core, composed mostly of iron, has been thought to be about 10 times greater than that of the rocky mantle. However, as Hofmeister shows on page 1699 (*1*), a reevaluation of the thermal conductivity of the mantle provides hope of a solution that "what the core giveth, the mantle taketh away."

To balance the power from the core, geophysicists have invoked mechanisms that either reduce the power of the core or return the excess power to the core. One mechanism requires that the core has an outside conductive layer (*2*). In another mechanism, called compositional convection, the presumed excess power drives impurities toward the center (*3*). These corrective models have complicated the description of the core's composition and thermal structure.

The problem centers on the mantle's thermal conductivity. This parameter describes how easily heat flows through the mantle. It can be separated into a radiative contribution, κ_{rad}, which is the flow of energy by radiation (as in a black body), and a lattice contribution, κ_{lat}, which is the energy flow through the minerals in the mantle.

Although well established in thermal physics (*4–6*), the contribution of radiation heat transfer at high temperature in Earth's mantle has not been effectively taken into account until now. In her research article, Hofmeister shows that κ_{rad} contributes substantially to deep Earth thermal conductivity and improves existing ideas of κ_{lat}. In equations for κ_{rad}, she includes the connection of photon and phonon lifetimes, assumed to be reflected in infrared peak widths; a few relevant measurements now exist for mantle minerals at high pressures and temperatures. She also determines the pressure (P) and temperature (T) dependence of the lattice thermal conductivity of insulators. The resulting value for κ is lower than previous estimates at low pressures and in the lithosphere (the crust and solid upper part of the mantle). A lower thermal conductivity requires a higher temperature gradient to balance the heat flow, and her results therefore necessitate a hotter lithosphere. But at the base of the mantle, Hofmeister obtains a thermal conductivity of 6.3 W m^{-1} K^{-1} (see the figure on this page), higher than the commonly accepted value for the deep mantle, 4.2 W m^{-1} K^{-1} (*7*).



Deep within Earth. The lower mantle (*3*), layer D'', and the outer core (*10*). Solid line, the temperature profile. Two values of κ are given for D'' next to the core (circled). The lower value, 4.8, is that calculated by Hofmeister, assuming that the composition of D'' is the same as that of the lower mantle. The upper value, 6.2, is that required to maintain a heat balance between D'' and the outer core. Q is power, the heat flow multiplied by the surface area.

How can this higher estimate be reconciled with our understanding of the heat flow between the core and the mantle? The boundary between the mantle and the core is known as the D'' layer (*8*). I will show that including D'' as the third component in the heat balance is the key to finding limits in the total power flowing from core to mantle and that this can be done without making special assumptions about the thermal structure of the core.

In determining the power balance, the first challenge is to estimate the power of the core and how much heat is transferred by conduction compared with convection, because this greatly affects the geodynamics. Most authors concerned with convection in the core have proposed that the convective power of the core is negligibly small (*9–11*). One suggestion is that the convective power of the core is 0.2 TW (*12*). The highest suggested value for core conductive power is 1/3 of the total power (*13*). The measured conductivity, κ, of D'' next to the mantle and the high thermal gradient across it require a high conductive power of about 5.4 TW in D''. This power must be exceeded by the total power from the core. Using 30% of the core conductive power for convective power, the total power leaving the core is 5.7 TW (4.4 TW conduction plus 1.3 TW convection), as shown in the figure on this page. The preferred solution implies that there is a convective flux of 0.3 TW in the D'' region near the mantle. In support of this interpretation, the D'' region has been suggested as an unstable, rapidly flowing region of low viscosity at the base of the mantle. This instability spawns plumes that rise through the man-

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